UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/724,857	12/01/2003	Donald E. Frail	PC 27833 (01459.US1)	2162

28880 7590 07/28/2005

WARNER-LAMBERT COMPANY
2800 PLYMOUTH RD
ANN ARBOR, MI 48105

EXAMINER	
GEMBEH, SHIRLEY V	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 07/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/724,857	FRAIL ET AL.	
	Examiner	Art Unit	
	Shirley V. Gembeh	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/01/2004, 6/14/20*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Information Disclosure Statement

The information disclosure statement (IDS) submitted on June 1, 2004 and June 14, 2004 has being considered by the examiner.

Claim Objections

Claim 1 is objected to because of the following informalities: In claim 1 line 5, piperldine should read piperidine, also pynmidinyl claim 11 line 8 should read pyrimidinyl. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The specification while being enabling for the method for treating said disorders include, without limitation, chronic and neuropathic pain, migraine therapy, urge, stress and mixed urinary incontinence. The compounds provided herein, are particularly useful in the treatment of these and other disorders due, at least in part, to their ability to selectively bind to the transporter 5 proteins for certain neurochemicals with a greater affinity than to the transporter proteins for other neurochemicals does not enable any person skilled in the art to which it pertains, or

which it is most nearly connected to practice the invention commensurate in scope with these claims does not reasonably provide enablement for prevention.

In evaluating the enablement question, several factors are to be considered. Note In re Wands, 8 USPQ2d 1400 and Ex parte Forman, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed and 8) the relative skill of those skilled in the art.

1) The nature of the invention: The method of use claims are drawn to preventing an individual from having chronic pain but no working examples are given to support applicants claim.

2) The state of the prior art: A study by Couch et al, Neurology (1976) 26 (121-127) that amitriptyline result section indicates page 123 shows that amitriptyline had a prophylactic effect that is not related to severity of migraine also see graph on page 123. The graph indicates that the prophylactic effects were unable to prevent headache (condition where there is pain).

3) The predictability or lack thereof in the art: Pharmacological activity in general is a very unpredictable area as discussed above. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

4) The amount of direction or guidance present and 5) the presence or absence of working examples: In addition there is no apparent guidance as to what to expect or how to extrapolate prevention that would 'a prion' have been expected to have produced the claimed result as claimed.

6) The breadth of the claims: The claims are drawn to methods of preventing,

7) The quantity of experimentation needed would be undue burden since there is inadequate guidance given to the skilled artisan for the reasons stated above.

8) The relative skill of those skilled in the art. Based on the unpredictable nature of the invention, one skilled in the art would not have envisioned practicing the invention without the exercise of undue experimentation budden.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims.

In consideration of each of factors 1-8, it is apparent that there is undue experimentation because of variability in prediction of outcome that is not addressed by the present application disclosure, examples, teaching and guidance presented. Absent factual data to the contrary, the amount and level of experimentation needed is undue and the resultant outcome not predictable.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Beck et al. (WO 01/32625) in view of Couch et a1. (reference ("AE") PTO 1449).

Beck et al. teach a method for treating "analgesia" which comprises administering a therapeutically effective amount of the claimed tetahydroisoquinoline compounds to a subject in need thereof (see the abstract, page 4, line 1 - page 18, line 31, page 2 1, line 12 and page 32, line 27). The difference between the Beck et al. reference and the claimed subject matter lies in that Beck et al. fail to expressly disclose a method for the treatment of chronic or neuropathic pain or of treating migraine headache. However, the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains because the term "analgesia" in Beck et :al. would have been reasonably interpreted as pain by one of ordinary skill in the art. This would be the case because analgesia" means the lack of pain, and thus it would not have been

reasonable to take the disclosure of Beck et al. to mean that the compounds would be effective to result in a lack pain. Given, therefore, that the reference discloses, in an unlimited manner, the treatment of pain, one of ordinary skill in the art would have been motivated to employ the compounds of Beck et al. for the treatment of pain in general and thus, would have recognized that pain of various etiologies, including pain lasting over a period of time, i.e., chronic pain of a neurological origin, i.e., neuropathic, or pain from headaches such as a migraine (see Couch et al. at page 122, column 1, penultimate paragraph, "unilateral pain, bilateral pain,, throbbing pain,, steady pain, and neck pain") would have been treated with a reasonable expectation that such pain would have been successfully achieved.

Claims 1-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Beck et al., US 6,579,885 ('885), in view of DeBernardis et al., US 5,389,638 ('638).

Beck et al teach methods of treatment of various neurological disorders (column 1 lines 7+ and stress disorder (claim 1) (column 14 line 35) administering the compound aryl and heteroaryl substituted tertadroisoquinoline column 2 line 52-53. Beck also teaches the moieties/derivatives attached to be effectively the same in claims 2-29, e.g. R^1 through R^8 is the same taught by Beck.

DeBernardis et al., teach, a pharmaceutical composition comprising (column 1 line 10) tetrahydroisoquinoline (abstract) to treat migraine (claim 1) column 1 line 16.

Beck did not per se teach treatment of headache, migraine or chronic neuropathic pain. The claims differ since the '885 patent uses phenyl substituted tetrahydroisoquinolines derivatives to treat various neurological disorders, and did not

per se teach of the treating headache or migraine, however migraine and headache is considered to be a neurological disorder, as taught by R. J. Schuerger © 2002 Migraine and Headache-Neurological Diseases and Disorders.

Beck et al,, however, teach the use of the pharmaceutical compound administering the compound aryl and heteroaryl substituted tertahydroisoquinoline column 2 line 52-53, i.e. the same compound administered in the claim by applicant.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of '885 and '683 since the compounds are structurally the same with effectively the same moieties, would administer it for the treatment of pain (migraine) since neurological disorder can also include pain (migraine/headache) for the same reasons as discussed above.

One of ordinary skill in the art would have known that using 4-phenyl substituted tetrahydroisoquinolines derivatives in place of heteroaryl substituted tertadroisoquinoline would work because is a well known compound for treatment of neurological disorders, and pain is classified as a neurological disorder. Therefore one of ordinary skill would have been motivated to combine the teachings of '8855 with that of '683 as disclosed for the treatment of chronic neuropathic pain. The cited prior art would have motivated one of skill in the art to select for chronic neuropathic pain.

One of ordinary skill in the art would have expected successful results for the treatment of chronic neuropathic pain. Thus the claims are deemed prima facia obvious over the cited prior art.

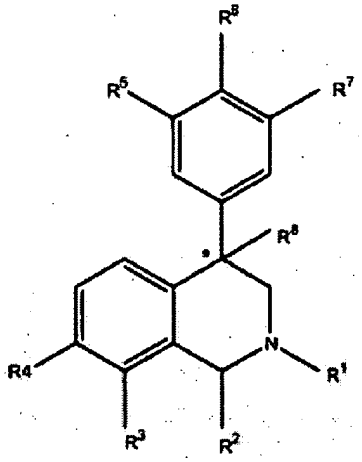
Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-29 are provisionally rejected under the judicially created doctrine of double patenting over claims 1-25 of copending Application No. 10,724,856. This is a provisional double patenting rejection since the conflicting claims have not yet been patented. Claim 1 has a compound of the following structure:



(I)

Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the copending application are to a pharmaceutical compositionreciting the identical structure which comprises of an active compound phenyl substituted tetrahydroisoquinolines. The moieties attached are effectively the same in the current and copending applications. The subject matter claimed in the instant application is fully disclosed in the referenced copending application, the only difference is in the use of treatment. With regard to claims 2-29 are effectively duplicates of claims 2-25 of the copending application.

Thus, claims 1-29 are directed to an invention not patentably distinct from claims 1-25 of co-pending application.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shirley V. Gembeh whose telephone number is 571-272-8504. The examiner can normally be reached on 8:30 -5:00 Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SVG
7/20/05

CHRISTOPHER S. F. LOW
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600